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Individualization of music-based rhythmic auditory cueing in Parkinson's disease

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Gait dysfunctions in Parkinson's disease can be partly relieved by rhythmic auditory cueing. This consists in asking patients to walk with a rhythmic auditory stimulus such as a metronome or music. The effect on gait is visible immediately in terms of increased speed and stride length. Moreover, training programs based on rhythmic cueing can have long-term benefits. The effect of rhythmic cueing, however, varies from one patient to the other. Patients' response to the stimulation may depend on rhythmic abilities, often deteriorating with the disease. Relatively spared abilities to track the beat favor a positive response to rhythmic cueing. On the other hand, most patients with poor rhythmic abilities either do not respond to the cues or experience gait worsening when walking with cues. An individualized approach to rhythmic auditory cueing with music is proposed to cope with this variability in patients' response. This approach calls for using assistive mobile technologies capable of delivering cues that adapt in real time to patients' gait kinematics, thus affording step synchronization to the beat. Individualized rhythmic cueing can provide a safe and cost-effective alternative to standard cueing that patients may want to use in their everyday lives.

Keywords: Parkinson's disease; rhythm; gait; individual differences; therapy

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease, and the most common serious movement disorder.[1] The disease affects 1–2% of older adults after 60 years of age.[2] Worldwide, about 4 million people suffer from PD, with more than 1.2 million only in Europe.[3] Unfortunately, these numbers will tend to increase as a result of the aging population. For example, the prevalence in Europe is estimated at 160 PD patients per 100,000 among people aged 65 and older; this number is forecasted to double by 2030.[4]

PD is characterized by a loss of dopaminergic neurons leading to the progressive reduction of speed (bradykinesia) and amplitude (hypokinesia) of all movements.[2,5] Dopaminergic drugs and neurosurgical treatments (e.g., deep brain stimulation) significantly improve these motor symptoms for several years.[6] After a period of relative stability, however, motor symptoms become more apparent and thereby progressively reduce patients' autonomy and worsen their quality of life.[7] Slowness of movement, limb rigidity, and postural instability bring about gait disorders, more apparent at late stages of the disease.[8] Parkinsonian gait is characterized by increased cadence (number of steps per minute), and reduced stride length and velocity, sometimes associated with freezing of gait.[9,10]

Gait disorders in PD are a major therapeutic challenge and a growing economic burden for the healthcare system[6]. The increased likelihood of falls[2,8] is a major reason for morbidity and disability in PD.[11] From 38% to 87% of PD

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patients experience falls, a recurrent phenomenon in the disease. Falling entails severe consequences, including head injuries, fractures (hip in particular), which in some cases may be fatal.[12] Falls also produce fear of new falls[13] that results in loss of independence, reduced mobility, increased osteoporosis, reduced social activity and depression.[14] Unfortunately, gait and balance disorders respond poorly to long-term dopamine replacement therapy.[6,15] These disorders are frequently less responsive to conventional PD treatments[16] than other symptoms, especially when the disease progresses.[10] Therefore, additional nonpharmacological interventions to improve gait in PD have been increasingly examined.[17]

Beneficial effects of rhythmic auditory cues

Rhythmic auditory cues can be used with success to improve gait in patients with PD, as found in several clinical studies.[18–21] External auditory stimuli, such as a metronome or music with a salient beat, provide temporally predictable cues to support gait initiation and continuation. Presentation of rhythmic cues has an immediate effect on walking in PD by increasing speed, stride length, and improving symmetry and stability.[22] Notably, the beneficial effects of rhythmic cues can carry over to noncued gait, after patients are submitted to a period of training with auditory cues. Training with rhythmic cues can result in increased mobility, enhanced quality of life, and a reduction of freezing episodes.[23–26] Rhythmic cues conveyed via music can be more efficient than stimulation provided with a simpler metronome, as found in healthy older adults.[27,28] Despite the fact that both music and a metronome have a common main beat, music is likely to exert a stronger effect on gait due to its complex texture including melody, harmony, and rhythmic structure (with multiple embedded periodicities); moreover, music ability to evoke emotions and increase motivation may further enhance its effect on walking.[28]

Based on the aforementioned encouraging findings, one may be tempted to use rhythmic cues for improving gait in PD in a systematic fashion. However, there are indications that the success of rhythmic cueing may vary significantly among individuals.[21,29] Rhythmic auditory cueing may not be the best strategy to improve gait for all patients. For example in a recent study in which 14 patients with PD were submitted to a 1-month music-based training with rhythmic auditory cues, only some patients positively responded to cueing (e.g., showing increased gait velocity). Others were either not influenced by the training or showed worsened gait performance (i.e., slower velocity) after the training period.[29] This variability of the effectiveness of cueing training is not totally surprising. PD is by definition very heterogeneous. Symptoms evolution and response to treatments vary considerably from one patient to another.[6] This heterogeneity has led neurologists to identify criteria for responsiveness to treatments, to determine the optimal treatment for each patient. A better understanding of the causes of such variability may shed light on the functional and neuronal mechanisms underlying the effects of rhythmic cueing. Moreover, it may lead to individualized treatment and more efficient gait training in PD.

Patients' response to rhythmic cues is linked to spared rhythmic abilities

What is the source of variability in patients' response to rhythmic cueing? Variable response to cueing may be linked to patients' variability in their rhythmic abilities. Tracking beat periodicity in a simple or complex auditory signal (e.g., extracting the beat of music) and aligning the steps to the beat are likely to play a critical role in walking to rhythmic cues. Responding to rhythmic auditory cues may build on relatively intact mechanisms supporting beat perception and synchronization. To coordinate steps with the timing and rate of the auditory stimulation, the patient must be able to extract the beat from an auditory sequence and to time movements to the beat onsets. Accordingly, it is expected that the ability to extract the beat from a rhythmic stimulus, to match gait cadence to stimulus rate, and the accuracy in aligning footfalls to the beat can predict the response to rhythmic cueing.

Beat tracking and synchronization skills vary considerably in the general population but even more in PD.[30–34] Patients with PD taken as a group show poor performance in a variety of perceptual and motor timing tasks.[35,36] They exhibit heightened variability in finger tapping to the sounds of a metronome,[37,38] and poor performance in beat perception tasks.[33,39] However, even in a group of patients with PD, which is quite homogeneous in terms of motor symptoms (i.e., with comparable severity), rhythmic abilities vary quite considerably.[29,33,39] Despite having PD, some patients reveal quite spared rhythmic skills that may allow them to benefit from an external temporally predictable cue.

Moving with an external rhythmic stimulus may compensate for patients' difficulty in internal generation of a beat,[39,40] by providing a temporal frame of reference for movement coordination such as step initiation. Rhythmic auditory cues are likely to foster stimulus-driven allocation of attention to relevant aspects of gait kinematics, thus enhancing temporal prediction of events (i.e., steps), and facilitating movement planning and initiation.[41–43] Hence, external rhythmic cues may be beneficial for patients with relatively spared rhythmic abilities such as good beat extraction and low variability in motor synchronization with a beat. Different brain circuitries may underpin this compensation process.[19,44] Generally, it is hypothesized that individual differences in the response to rhythmic cues reflect patients' ability to engage unimpaired (or partly spared) resources from networks subserving timing and motor control.[44–46] One possibility is that the malfunctioning of basal-ganglia-cortical circuitry in PD is compensated by the recruitment of alternative pathways spared by the disease. A reasonable candidate is cerebello-thalamo-cortical circuitry, typically affected only later during the progression of the disease.[19,33,44] There is evidence of enhanced cerebellar activity after gait training via rhythmic stimulation.[47] Interestingly, the cerebellum plays a critical role in coupling movement to temporally regular sequences of events,[48,49] and in predictive motor control.[50] Patients' spared abilities in synchronizing their steps to the beat of rhythmic stimuli, supported by this circuitry, may afford a positive response to the stimulation. Another neural network that is likely to participate in the effects of rhythmic cueing is basal–ganglia–cortical circuitry. Even if this network is impaired in PD, its residual activity could be sufficient to guarantee a minimal amount of beat processing[51,52] providing a temporal pacing of movement initiation and execution. Residual beat processing may thus allow some of the patients who show relative spared beat perception to benefit from rhythmic cues. To date, it is still unclear which of the hypotheses above (alternative network versus residual activity) is the most viable to account for the beneficial effects of rhythmic cueing. In both cases, however, it follows that the response to rhythmic cueing should be mediated by mechanisms involved in beat tracking and synchronization. The functioning of these mechanisms can be tested via beat perception and sensorimotor synchronization tasks.

That individual abilities in beat perception affect gait when participants synchronize with rhythmic stimuli was already shown in healthy young adults.[53] For example, walking to low-groove music appears as being detrimental to gait (i.e., leading to a reduction of cadence and step length) in particular for participants with poor beat perception. To date, it is unknown whether differences in the ability to track the beat of a rhythmic stimulus can affect the immediate gait response to rhythmic cueing in PD. We tackled this question in a recent study,[54] in which a group of 39 patients with PD (with average severity of motor symptoms, 2.0 ± 0.5 at Hoehn and Yahr stage) and 39 matched controls were asked to walk together with rhythmic stimuli. Stimuli were metronomes (i.e., sequences of isochronously presented tones with a triangle timbre) and four computer-generated musical excerpts (i.e., highly familiar military marches, such as Mozart's "Turkish March"). Music had a salient beat structure, was pleasant, and conducive to movement.[54,55] Rhythmic stimuli were individualized, as the beat rate was 10% faster relative to each participant's preferred cadence. Notably, no explicit instructions were provided to synchronize footfalls to stimulus beats.

Participants' ability to move to the beat of rhythmic stimuli was tested by computing the synchronization between heel strikes and the beat times. A synchronization score, from 0 to 1, also referred to as "synchronization consistency,"[32,57] indicated how well participants aligned their footfalls to the beats.[29,55,58] A score of 0 referred to lack of alignment between the footfalls and the beats while 1 indicated perfectly consistent alignment (maximal phase locking of the steps to the beat). Beat perception was tested with the Beat Alignment Test (BAT),[59] taken from the Battery for the Assessment of Auditory Sensorimotor and Timing Abilities (BAASTA).[34] In this task, participants detected whether a metronome superimposed on the musical excerpts (Bach's "Badinerie" and Rossini's "William Tell Overture") was aligned or not to the musical beat.

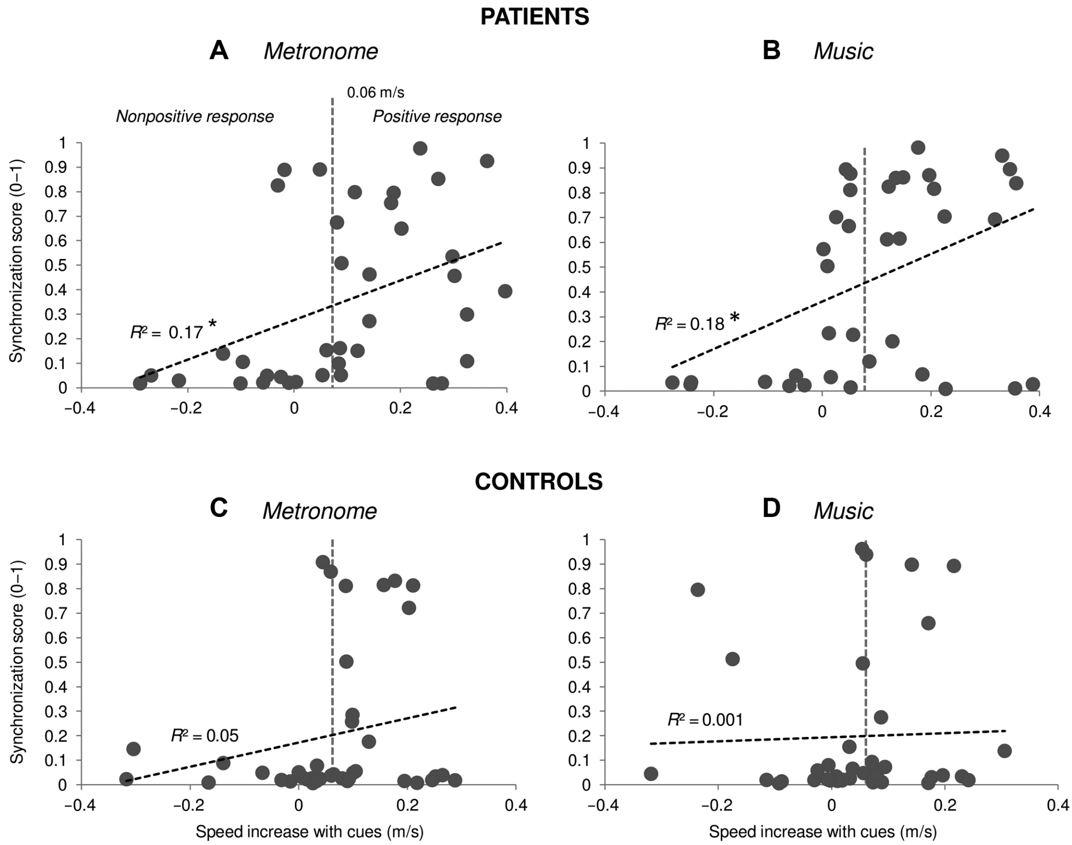

Figure 1. Individual data for patients with PD and controls, when walking with a metronome (panels (A) and (C), respectively), and with music (panels (B) and (D)). Synchronization of footfalls with stimulus beats (synchronization score) is presented as a function of response to cueing (increase in gait speed, namely gait speed with cues – gait speed without cues). The regression lines indicate whether the response to cueing significantly increased as a function of step synchronization to the beat. Participants' response to cueing is qualified based on a clinically meaningful increase in gait speed (>0.06 m/s).[60] $*P < 0.01$ or $P = 0.01$.

On average, both patients and controls benefitted from cueing, as their gait speed increased by 0.09 and 0.06 m/s, respectively, across cueing stimuli (main effect of cueing, $F(1,76) = 18.0$, $P < 0.001$; no interaction between cueing and group). In spite of this general and unsurprising result, however, patients and controls responded very differently to cueing when examined individually. In Figure 1, we display patients and controls' individual response to cueing, as indicated by the difference in gait speed when walking is cued relative to a noncued condition (baseline). The results were presented separately for metronome and music cueing stimuli. Positive values indicate that participants reacted to the cues by increasing their speed. Response to cueing is presented as a function of the synchronization between the steps and the beat of the stimuli. It can be seen that patients who benefitted most from the cueing were also those who displayed the highest synchronization to the cues (with the metronome, $R^2 = 0.17$, $F(1,36) = 7.4$, $P = 0.01$; with music, $R^2 = 0.18$, $F(1,35) = 7.7$, $P < 0.01$). This relation was not found in controls (with the metronome, $R^2 = 0.17$, $F(1,36) = 1.8$, $P = 0.18$; with music, $R^2 = 0.001$, $F < 1$). Notably, patients aligned their steps to the beat (synchronization score = 0.40) more often than controls did (synchronization score = 0.20; $t(73.7) = 3.0$, $P < 0.001$). Interestingly, patients and controls' response to cueing was comparable with metronome (gait speed for patients = 1.21 m/s; for controls, speed = 1.33 m/s) and music (for patients, speed = 1.22 m/s; for controls, speed = 1.31 m/s; no significant main effect of stimulus, $F(1,74) = 3.3$, $P = 0.07$, nor an interaction between stimulus and

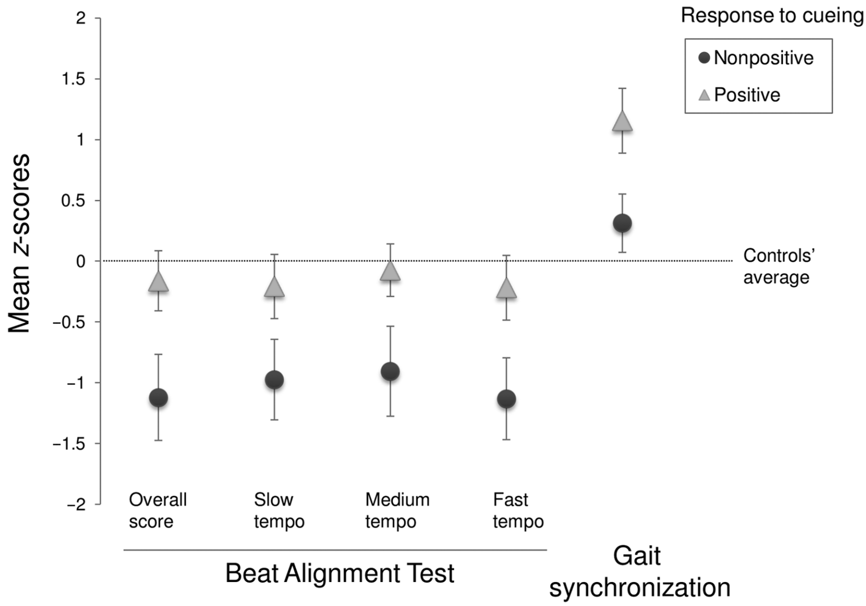

Figure 2. Performance of patients with positive response (light-gray triangles) and nonpositive response to cueing (dark-gray circles) in beat perception (BAT), and synchronization of footfalls to the beat. Mean performance is expressed in Z-scores relative to the average and SD of the control group. In the BAT, the overall performance and the performance with stimuli presented at the three tempos (slow, 750 ms; medium, 600 ms; fast, 450 ms) is presented. Error bars are SE of the mean.

group, $F(1,74) = 1.3$, $P = 0.26$). As gait speed with metronome and music stimuli was highly correlated (for patients, $r = 0.94$, $P < 0.0001$; for controls, $r = 0.86$, $P < 0.0001$), data were pooled across stimuli in the following analyses.

To better appreciate the differences in response to cueing, the smallest clinically significant difference in gait speed for PD patients (0.06 m/s) was used to categorize patients with positive and nonpositive response to the cues.[29,60] With that criterion, 17 patients displayed a nonpositive response to cueing, while 22 showed a positive response. Notably, six patients showed significantly worsened gait performance with slower gait velocity (–0.18 m/s, on average) in the presence of cues than at baseline.

By definition of the metric, patients with positive response to cueing increased their speed when cued (from 1.05 to 1.26 m/s). This was not observed in the other patients who basically maintained their speed regardless of the cues. What is more surprising, however, is that patients with positive response to cues also increased their stride by 14 cm (from 123 to 147 cm), while patients with negative response dramatically reduced their strides by 11 cm (from 132 to 121 cm). This is compelling evidence that rhythmic cueing can be very beneficial for some patients but deleterious for others. We related this distinction to patients' beat perception and synchronization profiles. To this end, patients' results from the BAT and synchronization performance, reported in Figure 2, were expressed as individual Z-scores relative to a reference distribution, that is, mean and SD of controls. Patients with positive response to cueing aligned their footfalls to the beat more often ($t(37) = 2.35$, $P = 0.01$) and showed better beat perception (on average, $t(23.7) = 2.02$, $P < 0.05$) than other patients. Note that beat perception for patients with positive response to cueing was relatively spared, as their performance was very close to the average of controls (i.e., with Z-scores not significantly different from 0).

These findings reveal important individual differences in the response of patients with PD to cueing and the relation of these differences to beat perception and synchronization skills. Patients with good beat perception and who are spontaneously aligning their steps to the beat benefit the most from rhythmic auditory cueing. Interestingly, these findings are unlikely to be confined to the immediate effects of rhythmic cueing. Indeed, they are in keeping with the results of a previous training study in which patients with PD were trained using music-based rhythmic stimulation.[29] In that study, performance in synchronization tasks (via tapping and gait) could be used to predict a positive response to the training, qualified via the same criterion as above (i.e., smallest clinically significant difference in gait speed). For example, patients showing low synchronization variability and a prompt response to a stimulation change during synchronization were highly likely to positively respond to the training. In sum, these findings suggest that beat tracking and synchronization skills of patients with PD should be taken into account, among other indicators (e.g., patients' willingness and motivation to walk and train more with music), to screen patients who are the most likely to benefit from rhythmic cueing. Notably, in some cases, even if the effect of cueing on gait speed is below the critical cutoff for clinical significance (without being deleterious), walking with music may still increase a patient's mobility and motivation to walk.

Bridging the gap: assistive mobile technologies can compensate for rhythmic deficits

In spite of the oft-reported beneficial effects of rhythmic cueing on gait in PD, it appears that some patients significantly worsen their performance when walking with cues. Deleterious response to rhythmic cues is linked to poor beat perception and reduced synchronization to the beat. Patients who are unable to align their steps to the beat may have to face a typical dual-task situation in which rhythmic cues would act as distractors impinging on reduced cognitive resources. Walking, a mostly automatic task in healthy adults, is particularly sensitive to a dual task in the elderly,[61–63] and even more in PD.[64,65] Note, however, that patients may still benefit from walking with music for other reasons that go beyond mere gait improvement. Music is a highly motivating stimulus acting on dopaminergic mechanisms and known for its ability to engage emotions and stimulate the reward system.[66,67] Walking with music may be a rewarding activity in itself, thus having beneficial effects like increasing mobility and the patient's quality of life. Whether the unwanted effects of rhythmic cueing on gait can be offset by other advantages will need to be assessed on a case-by-case basis by the clinician.

Given the variability in the response to rhythmic cues, an individualized approach is in order, especially if we want patients with poor rhythmic skills to benefit from cueing. A solution would be to provide individualized rhythmic stimulation that: (1) capitalizes on patients' spared rhythmic abilities, thus affording spontaneous synchronization to the beat if possible, and (2) assists the patient when these abilities are impaired. This can be represented in the simple schema presented in Figure 3. Assuming that individuals' rhythmic abilities can be put on a continuum, patients can more or less engage beat perception/synchronization mechanisms when walking with rhythmic cues. As stated, relatively spared beat perception affords spontaneous synchronization of the footsteps to the beat during rhythmic stimulation leading to the ensuing benefits. However, with the reduction of these abilities, an external stimulator will have to compensate for rhythmic deficits, by assisting the patient and eventually fostering synchronization of footsteps to the beat.

Individualized rhythmic cueing calls for the use of mobile technologies that can afford monitoring of motor behavior via dedicated sensors while delivering rhythmic stimulation, which adapts in real time to patient's performance. An appropriate mapping strategy has to be devised that adjusts the rhythmic stimulus to the movement properties in real time. This strategy will afford the patient to maintain step-to-beat synchronization regardless of the patient's rhythmic abilities, and thereby will allow maximizing the effect of external cueing. The underlying mechanism that is selectively targeted by this cueing strategy is audiomotor coupling (e.g., mediated by cerebello–thalamo–cortical circuitries), which seems to play a critical role in fostering positive effects of rhythmic auditory cueing both in immediate cueing,[54] and in cueing-based training programs.[29] A way to implement this mapping strategy is to model bidirectional coupling between the stimulus beat and the patient's step time, detected via dedicated sensors (e.g., accelerometers, or inertial measurement units). Along this line, existing mapping strategies implemented in systems, such as WalkMate[68,69] and DJogger,[70] have treated the phase of the stride (or step) cycle as a continuous dynamic process to which the stimulus

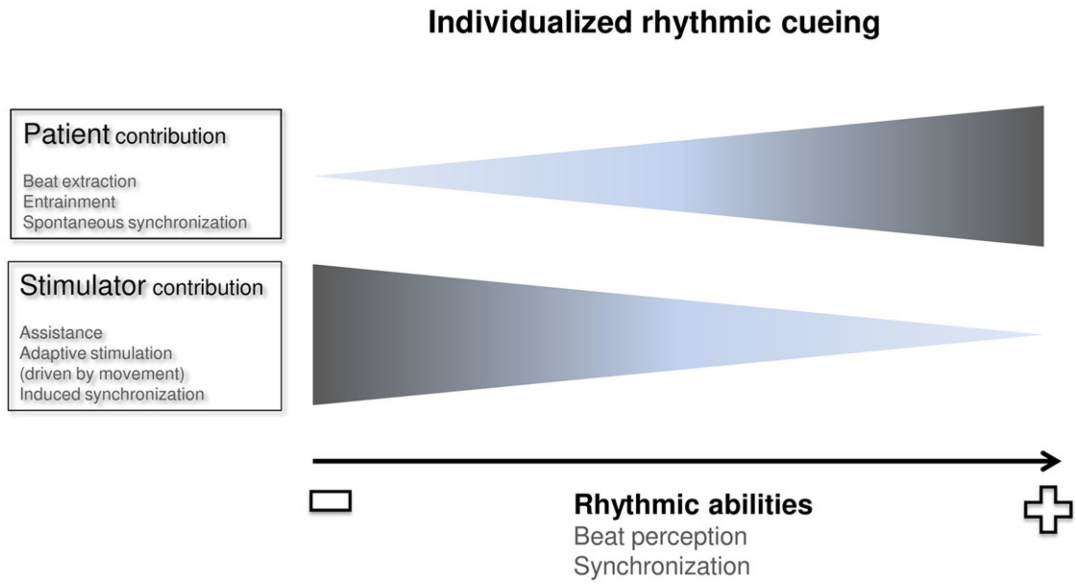

Figure 3. Schema illustrating the basic principles behind individualized rhythmic cueing for PD.

is adapted. Another possibility is model bidirectional coupling via mutual coordination that makes predictions about the conditions in which spontaneous synchronization of gait is more likely. Mutual coordination is expected to induce spontaneous entrainment and could overcome a degree of dissimilarity between gait and stimulus by entraining the participants to a faster cadence. Mutual synchronization for adaptive rhythmic cueing has been recently implemented in our laboratory as a system of two coupled oscillators, an instantiation of the Kuramoto system, a fundamental model of synchronization previously applied to a wide range of biological and neural processes.[71–73] This solution has the advantage that it is individualized by tailoring the stimulation to the patient's cadence, thus keeping step-beat synchronization, while driving the patient toward an optimal value (i.e., higher cadence). This form of individualized rhythmic cueing using music stimulation is presently implemented in mobile technology and being tested with patients with PD (BeatHealth project, http://www.euromov.eu/beathealth/).

Conclusions

Rhythmic auditory cueing to improve gait in PD has variable success across patients. Whether a patient benefits from the stimulation is likely to depend on patients' perceptual and sensorimotor rhythmic abilities. These abilities are sustained by both residual activity of impaired neuronal circuitries (basal ganglia–thalamo–cortical networks) and by alternative functional pathways (cerebello–thalamo–cortical networks). There is growing evidence that relatively spared abilities to track the beat favor a positive response to rhythmic cueing. This was shown by patients' spontaneous tendency to align their footsteps to the beat (an implicit measure), and by their ability to detect whether a metronome was aligned or not to the beat of music (an explicit timing measure). It will be interesting in future research to assess whether the link between beat perception and a positive response to cueing is also visible with an implicit timing task.[74] When these conditions are missing, most patients either do not respond to the cues or experience deleterious effects on gait (e.g., shortened strides), which can increase risk of falling and dependency. It is still unknown whether patients with poor rhythmic abilities rely in particular on alternative pathways to compensate for their timing deficits, a possibility that awaits further research.

Individualized rhythmic cueing can be achieved via assistive mobile technologies compensating for rhythmic deficits by delivering cues that adapt in real time to patients' gait kinematics. These solutions promise to provide a cost-effective, everyday usable, upgrade to standard cueing and potentially maximize its long-term effects.

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Competing interests

The authors declare no competing interests

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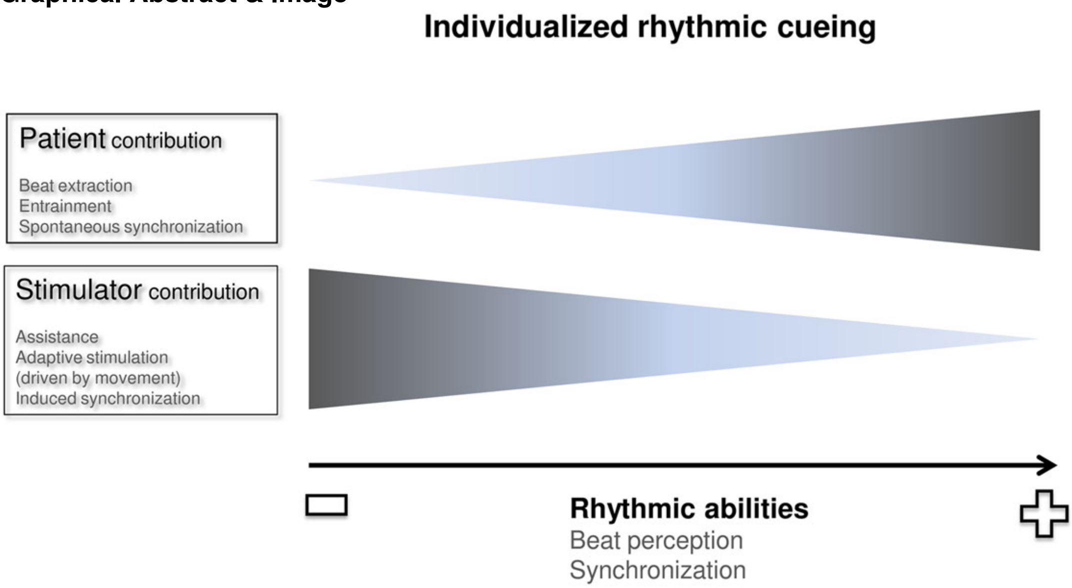
Graphical Abstract & Image



Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease, and the most common serious movement disorder. Gait dysfunctions in PD can be partly relieved by rhythmic auditory cueing. This consists in asking patients to walk with a rhythmic auditory stimulus such as a metronome or music. The effect on gait is visible immediately in terms of increased speed and stride length. This paper describes training programs based on music-based rhythmic cueing and their long-term benefits in PD patients.